REMARKS

Claims 1-5, 9-13, 16-35, 39-43 and 46-51 were rejected under 35 U.S.C.§112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.The Examiner pointed to the recitation of the terms "USDP" and "Ph.Er." as making the claims inderfinite.

Reconsideration is requested.

The terms "USP" and "Ph.Er." have been deleted from the claims and thus this ground of rejection has been rendered moot.

Claims 1-2, 4-5, 9-13, 16-20, 22-35, 39-43, and 46-61 were rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the written description requirement in that the term "weight" had been introduced into the claims. By this Amendment, the terms "ratio of active ingredients ...is in the range of 100:2.5 to 100:30 by weight" have been deleted from claim 1. The term "weight" has been deleted from the other claims where it was used in connection with the term :ratio".

The applicant believes the the rratios recited in claim 1 are not necessary to point out the invention as the invention resides in the novel combination of materiasl and not in a numerical ratio. Thus amended claim 1 points out the invention is clear and concise terms. The Examiner stated that the term "ratio" as used in the claims is not described in the specification such a way as to reasonably convey to one skilled in art. It is the applicant's position that the term ratio as

used in the present application is readily understood by one skilled in the art to reflect weight ratios. In the pharmaceutical arts, solid dosage forms are only formulated by weight and not by volume and thus the ratios would be always understood to be by weight and further please also refer following paragraph of the specification, which also clearly says that in the instant invention, excipients are used in the dosage form in a weight proportion.

"[0050] The quantity of commonly used excipients in oral pharmaceutical formulations used is from about 2% to about 500% by weight, preferably from 2 to 100% more particularly 10 to 60% based on the total dry weight of the polymer".

This is further substantiated by all of the examples. The Examiner has not cited any reference to show that any ***solid*** pharmaceutical dosage is formulated by volume and not by weight. The specification in the present application is directed to highly educated and highly skilled scientists who can instantly recognize that weight ratios are what are described. In any event, if it ever became necessary, it would only take a few simple experiments to determine if a volume ratio could possibly have been intended to be described. It is well established that routine experimentation may be required to practice a patent without making the patent non-enabling and thus there is no requirement that the most minute details be recited in a patent application. Original claims 28 and 47 point out specifc weights of the ingredients and these claims are free of of any objection as to the use of the term ratio. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1-5, 9-13, 16-23, 25-26, 30-35, 39-43 and 46-60 were rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins et al. (Timmins).

Reconsideration is requested.

It is known in the pharmaceutical arts that many modified delivery systems utilize a matrix dosage form that provides for the controlled release of sparingly soluble drugs to insure the delivery of pharmaceuticals at a specified rate. For highly soluble drugs, these matrix formulations do not provide adequate control over the release rate and result in a drug release profile that approximates first-order kinetics and often results in dose dumping or a burst release that makes the matrix formulation unacceptable for use with soluble drugs. However, since many modified release dosage forms contain comparatively large amounts of a highly soluble active ingredient it is often necessary to include large amounts of suitable excipients to achieve appropriate controlled release profiles. This results in an over sized dosage form which causes patient rejection due to the difficulty in swallowing the over sized dosage form. This is also acknowledged by Timmins. Hence a technique is needed, which can effectively control the release of the highly soluble active ingredient without requiring an over sized dosage form.

The Timmins patent discloses a biphasic controlled release delivery system for highly soluble drugs such as metformin hydrochloride, which has prolonged gastric residence and that swells following hydration. The major limitation of the Timmins dosage formulation is that it provides a very bulky formulation for higher doses of the metformin hydrochloride that is very inconvenient for human consumption. For instance, the cited example provides a formulation of 500mg metformin with a tablet weight of approx. 1.0gm.

It is apparent from the Timmins specification that the Timmins dosage formulation operates by increasing the time that the dosage remains in the stomach because the dosage formulation is designed to swell in the stomach so that the dosage

formulation will have a prolonged residence time. This essential functional characteristic can only be achieved by the use of polymers that swell on contact with water. (Cf. Timmins col. 20, lines 55-60). Therefore, although Timmins has disclosed a dosage formulation having an inner solid particulate phase and an outer solid continuous phase that uses one or more hydrophilic polymers, one or more hydrophobic polymer and/or one or more hydrophobic materials, the Timmins composition must contain at least one hydrophilic polymer, as shown by reference to all of the enabling examples of that patent. Hence, in the implementation of the teachings of Timmins, a skilled person in the art would be directed to use at least one hydrophilic polymer in following the teachings of Timmins as to the making a sustained release formulation. Hence, claim 1 and the claims that are dependent on claim 1 of the present application point out a formulation which contains only hydrophobic polymers which are not made obvious by the Timmin patent. Hence, Timmins does not make the instant invention obvious. Claim 1 specifically recites micromatrix particles that use only hydrophobic polymers to prepare the sustained release dosage form.

Furthermore, it is not disputed that matrix formulations of highly soluble drugs will require high amounts of polymers to achieve a controlled release profile. This results in an increase in the size of the dosage form as acknowledged by Timmins but this does not suggest any solution such as the dual retard technique pointed out in the claims of the present application. Thus, Timmins does not teach how one can reduce the overall size of dosage form while incorporating high amounts of drug in the composition.

In Timmins, the final size of the dosage form becomes very large due to large quantity of polymer required and thus the Timmins approach to the making of a useful formulation of a

drug that must be administered in high doses (i.e. 1000mg), such as metformin, the Timmins approach is not practical due the difficulty the patient will have in swallowing a very large size dosage form. This problem is exacerbated in older patient populations who often take these medications. The instant invention, as pointed out in claim 1, is directed to a dosage form containing a high solubility active ingredient in a sustained release form. Thus, if Timmins approach of formulation is adopted the final dosage form will become very large and cannoy be ingested by many if not all patients.

The following Table is derived from Timmins and it illustrates the high amounts of polymer relative to the active pharmaceutical ingredient (API) that result from the Timmins technique.

Example-1	500g API + 376.5g polymer	75% polymers by wt of API
Example-2	500g API + 391g polymer	78% polymers by wt of API
Example-3	500g API + 408 g polymer	81% polymers by wt of API
Example-4	500g API + >400 g polymer	81% polymers by wt of API

If we compare examples for the preparation of micromatrix particles of the same drug as shown in the present specification (e.g. Example 8-10 21-25% polymer), the final size of the dosage form will actually be much smaller as compared to the Timmins dosage form. This will make it possible to restrict the size of the dosage form of high solubility drug in sustained release form. This is clear from all the examples of the Timmins, which

only contains 500mg of drugs, whereas with instant invention it has become possible to prepare dosage form of 1000mg of active, while keeping the size of final dosage form suitable for swallowing.

While the disclosed range of polymer in Timmins seems overlapping to the claimed invention, Timmins actually does not teach the sustained release formulation of high solubility drug using a reduced quantity of polymers by using dual retard techniques.

Thus, it is clear that, if the teachings of Timmins are applied, any person skilled in art would end up making a large sized dosage form for highly soluble drugs.

As mentioned above another common problem with a modified release dosage form of a highly soluble drug is dose dumping which is essentially a burst effect in-vivo.

In the present specification at paragraph [0063], it is disclosed that: "FIGS. 2 and 3 show release of high solubility active agent 5 & 6 and 9 & 10 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique and release of high solubility active agent 7 & 8 and 11 & 12 as per example 3 & 4 respectively from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms inspite of that the figures clearly shows that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility active ingredient for prolonged period. FIG. 4 shows release of high solubility active agent 13 & 14 as per example 8 from a dosage form prepared using dual retard technique and release of high solubility active agent 15 & 16 as per example 11 from a dosage form

prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms. Inspite of that the figures clearly show that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility antidiabetic active ingredient for prolonged period."

The quoted section of the specification indicates that to achieve a desired release profile without having a burst effect, it is necessary to use a reduced amount of polymers in the dual retard technique as it is employed in instant invention for the preparation of micromatrix particles, as recited in the claims of the present application.

Timmins teaches a drug delivery system which achieves extended gastric residence by virtue of size but does degrade in vivo so as not to cause obstruction of the gastrointestinal tract. Thus, Timmins is strictly limited to gastroretentive dosage forms and teaches away from any other type of dosage form that does not swell in the stomach in order to retard its passage in the gastrointestinal tract.

This discovery is also confirmed by all of the examples of Timmins, who used very high amounts of polymers to achieve a useful controlled release profile for highly soluble drugs. This is achieved by the dual retard technique even though substantially reduced quantities of polymers are used, which results in a compact dosage form, which is convenient for swallowing.

An additional example of a particular drug that is amenable to formulation according to the claimed invention is sustained release Levetiracetam (Highly soluble drug) which is approved by FDA as a 500mg tablet for once daily administration.

However the approved dosage and administration starts with 1000mg daily and hence two tablets of 500mg must be taken by the patients, which is inconvenient to the patients. This appears to be a direct result of the large size that would result if prior art technology was used to formulate a 1000mg. In case of instant invention due to the very low quantity of polymer required, the same high solubility drug having high dose (Levetiracetam) can be prepared with acceptable size even with 1000mg strength. (This dosage form is being marketed in India as 1000mg Sustained Release tablet by applicant using the claimed inventive technology) This clearly shows the advantage of the technology of the present invention.

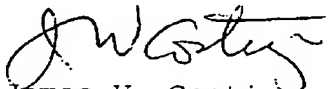
Thus, Timmins et al does not teach such a technique for high solubility drugs, which reduces burst effect and also reduces the size of the dosage form.

For these reasons, Timmins does not teach the claimed dosage form of the claims which is a ***a, high solubility active ingredient***, as a modified release, which uses a reduced quantity of polymers to control the release of a high soluble drug while providing a compact dosage form suitable for swallowing.

Timmins has been distinguished from the claimed invention above. As mentioned any skilled artisan using the teachings of Timmins would end up having large size of the dosage form even with Valproic acid & Niacin Drugs like Valproic acid and niacin do not have an absorption window and hence the teachings from Timmins can not be applied to these drugs. Hence it is respectfully submitted that claims 24, 27-28, and 29 are not obvious under 35 USC 103(a) over Timmins and Merck Index.

An early and favorable action is earnestly solicited.

Respectfully submitted,



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